## REMARKS

This response is filed with a petition for a two-month retroactive extension of time and with an appropriate fee. A Request for Continued Examination is also filed herewith.

Claims 2-6, 8-11, 17, 18, 20 and 24 are pending. Claims 12-6, 8-11, 17, 18, 20 and 24 have been rejected in the present application.

Claim 2 has been amended to include a more explicit reference to the oligonucleotides that hybridize to SEQ ID NO: 1 and SEQ ID NO: 4. Support for these amendments are found throughout the specification. For example, support for "wherein one or more uridine (U) nucleic acids are substituted for thymidine (T) nucleic acid bases in SEQ ID NO: 1 or SEQ ID NO: 4" is found at, for example, on page 15, paragraph [0036]. Support for the amendment regarding the stringency conditions and the hybridization of oligonucleotides is found, for example, on page 2, paragraph [0006]-[0009]; page 8, paragraph [0020]; page 15, paragraph [0036].

Claims 3-6, 8-11, 17, 18, 20 and 24 have been amended to more explicitly define the invention. No new matter has been added by virtue of these amendments and their entry is respectfully requested.

Any amendments and cancellation of the claims are not to be construed as an acquiescence to any of the rejections/objections set forth in the instant Office Action, and were done solely to expedite prosecution and allowance of the application. Applicants reserve the right to pursue the claims as originally filed, or substantially similar claims, in this or one or more continuation patent applications.

*Claim Rejections under 35 U.S.C. § 112.*

Claims 2-6, 8-11, 17, 18, 20 and 24 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully traverse. Applicants have fully identified and characterized the protein named pKe#122. (See, for example, paragraphs [0027]-[0065]). Applicants have identified the cell source (see, for example, paragraphs [0027]-[0028]); set up cell cultures for physical and functional characterization (see, for example, paragraphs [0027]-[0030]); isolation of mRNA (see, for example, paragraphs [0030]-[0031] and [0052]-[0054]); establishing a gene bank and sequencing (see, for example, paragraphs [0032]-[0036]); amino acid sequence identification (see, for example, paragraphs [0037]-[0038]); specific antibody production (see, for example, paragraphs [0039]-[0042]); detection of activated state of keratinocytes (see, for example, paragraphs [0043]-[0051]); vectors expressing pKe#122 and fusion proteins of variants thereof (see, for example, paragraphs [0055]-[0060]): anti-sense oligonucleotides and differentiation of cells (see, for example, paragraphs [0061]-[0065]). Therefore, one of ordinary skill in the art, based on the teachings of the Applicants, can select nucleotide sequences , wherein the sequences "are more than 8 nucleotides and hybridize these sequences under conventional stringent conditions." These sequences can be selected or discarded based on whether these sequences also have the same function as pKe#122.

In order to expedite prosecution, Applicants have amended the claims to conform with 35 U.S.C. § 112, first paragraph.

In view thereof, the reconsideration and withdrawal of the rejection are requested.

{WP258184;1}

Claim 18, is additionally rejected under 35 U.S.C. § 112, first paragraph. Applicants respectfully traverse. However, in order to expedite prosecution, Applicants have amended claim 18. Applicant's amendment is deemed to overcome the Examiner's rejection.

The Examiner has cited Probst *et al.*, *TIGs* Vol. 12(8):290-291, 1996; Harris *et al.*, *TIGs* Vol. 12(10):400-405, 1996; and *Science*, Vol. 269:1050-1055, 1995, to indicate that anitsense technology is unpredictable. However, Applicants have provided the details necessary to make and use the invention. Applicants have fully identified and characterized the protein named pKe#122. (See, for example, paragraphs [0027]-[0065]). Applicants have identified the cell source (see, for example, paragraphs [0027]-[0028]); set up cell cultures for physical and functional characterization (see, for example, paragraphs [0027]-[0030]); isolation of mRNA (see, for example, paragraphs [0030]-[0031] and [0052]-[0054]); establishing a gene bank and sequencing (see, for example, paragraphs [0032]-[0036]); amino acid sequence identification (see, for example, paragraphs [0037]-[0038]); specific antibody production (see, for example, paragraphs [0039]-[0042]); detection of activated state of keratinocytes (see, for example, paragraphs [0043]-[0051]); vectors expressing pKe#122 and fusion proteins of variants thereof (see, for example, paragraphs [0055]-[0060]); anti-sense oligonucleotides and differentiation of cells (see, for example, paragraphs [0061]-[0065]). Further, there was high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known. Therefore, the application provides sufficient guidance to the skilled artisan to conduct antisense therapy without any undue burden and with a reasonable expectation of success. The Examiner asserted that there is no prior art on the nucleic acid molecules encoding pKe#122, the pKe#122 protein itself, or on the function of this protein. However, the examiner concluded that there is no recognition in the prior art that pKe#122 is involved in any way in any dermatological disorder because pKe#122 had not jet been associated with any dermatological disorder. Applicant respectfully traverses and guides the Examiner's attention to the disclosure of the application itself. Applicant found that pKe#122 was

increasingly expressed in keratinocytes which are in an activated state, wherein "activated state" is define as a state of proliferation and/or migration, e.g. after skin injury or an antoimmunologically induced bullous dermatoses called Pemphigus vulgaris or Bullous pemphigoid (see paragraph [0100] of the description). Additionally, pKe#122 protein is increasingly expressed in the well-known and well-established HaCaT cell line (see paragraph [0041] of the description). HaCaT cells are known as human skin keratinocytes, which are spontaneously immortalized. As immortalization is considered to be the initial stage in human carcinogenesis in vitro (see enclosed abstract of Fusenig, NE. and Boukamp, P., (1998), *Mol. Carcinog.* 23(3):144-58), HaCaT cells are a suitable in vitro model for dermatological diseases or irritations of the human skin which require cosmetic treatment. Therefore, the skilled artisan has a reasonable expectation to carry out in vivo antisense oligonucleotide therapy successfully when following the guidance of the application.

Applicants describe the anti-sense oligonucleotides in detail and provide a working example, which provides antisense oligonucleotides and shows that the administered antisense oligonucleotides were effective in differentiating keratinocytes. Applicants also disclose appropriate conditions for administering the oligonucleotides. (See, for example, Example 6, paragraphs [0061]-[0065]):

> Influencing of keratinocytes with pKe#122-specific anti-sense oligonucleotides
>
> [0062] Anti-sense nucleotides are absorbed by cells, also keratinocytes (compare G. Hartmann et al. 1998: Anti-sense-Oligonukleotide, Deutsches Ärzteblatt 95, Issue 24, C1115-C1119), and bind to the mRNA present in the cell, inhibiting its translation, and hence expression (compare Y.-S. Lee, et al. 1997: Definition by specific anti-sense oligonucleotides of a role for proteinkinase C* in expression of differentiation markers in normal and neoplastic mouse epidermal keratinocytes, Molecular Carcinogenesis 18, pp. 44-53). Suitable anti-sense oligonucleotides were manufactured using the pKe#122-specific nucleotide sequence (SEQ ID NO:1 or SEQ ID NO:4). They were set to a concentration of 100 *M with a suitable buffer medium (so-called

"oligobuffer"). HaCaT cells were cultivated at 37*C and 7% CO2 up to a confluence of 70-80%. The cells were trypsinated off (10 minutes, 0.2 % EDTA, 5-10 minutes, 0.1 % trypsin) and set to a concentration of 25,000 cells/ml. 100 *l cell suspension (corresponds to 2,500 cells) was pipetted in per well of a 96-well plate. The cells were incubated for 1 hour, followed by the addition of the anti-sense oligonucleotide (2 *l of a 100 *M solution) and further incubation for 24-48 hours. The negative control consisted of cell batches to which was added an oligonucleotide with the same base distribution, but a randomly selected sequence.

[0063] The cells treated in this manner were analyzed under a microscope for phenotypic changes in the cells. The result of the microscopic analysis is shown on Fig. 12 and Fig. 13: Fig 12 a shows sub-confluent HaCaT cultures that were treated with pKe#122-specific anti-sense oligonucleotides, Fig. 12 b shows sub-confluent HaCaT cultures treated with control oligonucleotides, Fig. 13 a shows confluent HaCaT cultures treated with pKe#122-specific anti-sense oligonucleotides, Fig. 13 b shows confluent HaCaT cultures treated with control oligonucleotides, and Fig. 13 c shows a detail section from Fig. 13 a.

[0064] The results of microscopic analysis demonstrate that, in comparison to control oligonucleotides, the number of cells in the cultures treated with the specific anti-sense-oligonucleotide is distinctly reduced. This allows us to conclude that the cellular proliferation was diminished by the anti-sense-oligonucleotide. After confluence had been reached, the HaCaT cultures treated with anti-sense-oligonucleotides exhibited greatly enlarged cells, which were not discovered in the cultures treated with control oligonucleotides. These large cells correspond to differentiated keratinocytes in terms of their morphology. The findings allow us to conclude that cells treated with pKe#122-specific anti-sense-oligonucleotides show an increased tendency toward differentiation.

[0065] In summary, the treatment with pKe#122-specific oligonucleotides has a distinct influence on proliferation and differentiation.

Applicants further teach that which dermatological diseases showed the elevation of pKe#122. See, for example, paragraphs [0043]-[0046]. In particular, paragraphs [0044]-[0045] teach:

[0044] A cryotom was used to manufacture 5 µm thick frozen sections of tissues from skin biopsies of clinically unpathological, normal skin and clinically pathological, lesional skin owing to the diseases Pemphigus vulgaris, Bullous Pemphigoid and Psoriasis vulgaris. These are dried at room temperature and fixed in 100% acetone (100% methanol, 100% ethanol or 4% paraformaldehyde can be used instead of acetone). The sections are then treated according to the „blocking procedure" known in prior art to block non-specific binding sites for the antibody. In this example, two blocking steps are performed: (1) blocking with avidin/biotin and (2) blocking with normal serum. In the first blocking step, the avidin/biotin blocking was performed using the avidin-biotin blocking kit from Vector Laboratories according to the manufacturer's instructions, i.e., incubation was performed at room temperature initially for 15 minutes with the avidin finished solution, and then 15 minutes with the biotin finished solution. Subsequently, the sections were incubated with 10 vol.% normal serum in PBS (normal serum of species from which the second antibody originates, here goat normal serum; PBS = phosphate buffered saline, pH 7.2-7.4) for 15 minutes at room temperature.

[0045] After blocking, the sections in PBS are incubated for 1 hour at room temperature with a content of 5 µg/ml anti-peptide pKe#122-1. To remove the unbound antibody, the sections are then washed in PBS with a content of 0.2% (weight/volume) bovine serum albumin. This is followed by incubation, for example with a biotin-labelled antibody from the goat against rabbit IgG (1:500 diluted in PBS/0.2% BSA; 30 minutes at room temperature), another washing step and the application of a streptavidin labelled with the fluorescent dye Cy3 (1:1,000 in PBS/0.2% BSA diluted). A fluorescent dye other than Cy3 can also be used to mark the streptavidin, e.g., FITC. After the last washing step, the sections are covered with a covering agent, e.g., elvanol or histogel, and then analyzed and evaluated under a fluorescence microscope. Fig. 5 shows the results obtained from an immune fluorescence detection performed in this manner: The anti-pKe#122-1 IgG antibody staines keratinocytes on normal skin sections in the area of the epidermal basal membrane zone (Fig. 5A). When dying biopsies of lesional skin caused by the diseases Pemphigus vulgaris (Fig. 5B), Bullous Pemphigoid (Fig. 5C) or Psoriasis vulgaris (Fig. 5D), a distinctively strong coloration is observed in epidermal keratinocytes, in particular in the area of epidermal lesions. Hence, an increased expression and evident upward adjustment of the pKe#122 protein took place there. (Emphasis added).

{WP258184;1}

The Examiner's assertions that pKe#122 is not involved in "dermatological disorder" is incorrect as shown by the Applicants teachings above. That is, clinical specimens from patients with different dermatological diseases, showed an increase in pKe#122.

Applicants further disclose methods for treatment of epidermal diseases. See for example, page 8, paragraphs [0020]-[0025]:

> [0020] Protein pKe#122 and the polypeptides related thereto, i.e., to the amino acid sequence indicated in the SEQ ID NO:2 sequence protocol or SEQ ID NO:3 sequence protocol, specifically the polypeptides that can be derived through substitution, deletion, insertion and/or inversion from one of these amino acid sequences according to SEQ ID NO:2 or SEQ ID NO:3, or that have an amino acid sequence resulting from a splice variant of an mRNA, which is identical or complementary to the nucleotide sequence indicated in the SEQ ID NO:1 sequence protocol or the SEQ ID NO:4 sequence protocol, or to a partial sequence of these nucleotide sequences, or at least hybridized, offer numerous applications in the area of dermatological research and development. In particular, antibodies can be developed against these polypeptides or proteins, which then can be correspondingly modified for use either as diagnostic or therapeutic agents, or as cosmetic agents ("cosmeceuticals"). (Emphasis Added).
>
> [0021] Consequently, the invention also encompasses the use of such a protein or polypeptide for manufacturing a (monoclonal, polyclonal or recombinant) antibody against this polypeptide, the aforementioned antibody itself, and also its use for the diagnostic and/or therapeutic treatment of dermatological diseases, for the cosmetic treatment of the epidermis, and for the diagnostic, therapeutic and/or cosmetic treatment of other tissues or organs that express protein pKe#122. (Emphasis Added).
>
> [0022] According to more recent scientific knowledge, sense and/or antisense oligonucleotides are also possible as active agents for pharmacotherapy (compare G. Hartmann *et al.* 1998: Antisense Oligonucleotides, Deutsches Ärzteblatt 95, Issue 24, C1115-C1119), and

> also as active agents with a fundamentally new operating principle in pharmacotherapy. (Emphasis Added).
>
> [0023] Therefore, the present invention also relates to the use of sense or antisense oligonucleotides according to the invention for diagnostic and/or therapeutic treatment, in particular of dermatological diseases, or for the cosmetic treatment in particular of the epidermis.
>
> [0024] One technically and economically important potential application for a polypeptide according to the invention or a nucleic acid according to the invention also involves not least the fact that such a molecule can be used in a screening procedure to isolate materials from a very high number of provided materials that specifically bind to the respective nucleic acid or respective polypeptide. These substances can then serve as the parent material (lead structure) for the development of substances for use in pharmacology, and hence offer the preconditions for the development of alternative pharmaceuticals for diagnosis and therapy, in particular with respect to the dermatological diseases mentioned at the outset. (Emphasis Added).
>
> [0025] In this regard, the invention also relates to the application of a polypeptide according to the invention or a nucleic acid according to the invention for identifying substances that can be used in pharmacology, which bind to the polypeptide or nucleic acid, thereby influencing its/their function and/or expression, in particular exerting an inhibiting or activating effect.

Applicants submit that the invention is well demonstrated and sufficient to enable one of skill in the art to make and use the invention without undue experimentation. See, for instance, the Manual of Examining Procedure at Section 2164.02 which states:

> Compliance with the enablement requirement of 35 U.S.C § 112, first paragraph does not turn on whether an example is disclosed. An example may be 'working' or 'prophetic'.
>
> An applicant need not have actually reduced the invention to practice prior to filing (*Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987).

Also see, for instance, the Manual of Examining Procedure at Section 2165.02 which states in pertinent part:

> There is no statutory requirement for the disclosure of a specific example - a patent specification is not intended nor required to be a production specification. *In re Gay*, 309 F.2d 768, 135 USPQ 311 (CCPA 1962)

In summary, the disclosure of the pending application has to be regarded as sufficient to enable the skilled artisan to carry out the invention without any undue burden or undue experimentation. The skilled artisan, while using his general knowledge and the information provided by literature, together with the disclosure of the pending application was able to conduct *in vivo* antisense nucleotide therapy efficiently.

In view thereof, reconsideration and withdrawal of the rejection is respectfully requested.

***Claim Rejections under 35 U.S.C. § 102***

Claims 2 and 3 were rejected under 35 U.S.C. § 102(b) based upon a public use or sale of the invention.

The Examiner raises this rejection based upon a public use or sale of the invention because the cited reference Boehringer Mannheim Catalog 1997, page 95 shows that random hexanucleotides were available for sale as early as 1997. Independent claim 2 (claims 3 and 5 being dependent claims to claim 2) has been amended in order to overcome this rejection. Claim 2 is directed to oligonucleotides which hybridize to SEQ ID NO: 1 and SEQ ID NO: 4 under specified hybridization conditions. See, for example paragraphs [0006]-[0009]. That is, an oligonucleotide that will only hybridize under high stringent conditions would mean that the homology between the oligonucleotide would not encompass hexanucleotides as cited in the Boehringer Mannheim Catalog.

Claims 2 and 3 were rejected under 35 U.S.C. § 102(b)as being anticipated by Mierendorf *et al.* (U.S. Patent 5,629,179).

Applicants respectfully traverse.

Mierendorf *et al.*, teach the generation of random primers. Mierendorf *et al.*, do not teach or disclose which random sequences will hybridize to SEQ ID NO's: 1 and 4; which conditions would be necessary to achieve hybridization to SEQ ID NO: 1 and SEQ ID NO: 4. Therefore, undue experimentation would be required. By reading Mierendorf *et al.*, one of ordinary skill in the art would not arrive at the instant invention. Applicants submit that Mierendorf *et al.*, do not teach each and every limitation of claims 2 and 3. Furthermore, claim 2 has been amended to more clearly define the conditions of hybridization of nucleic acid oligonucleotide hybridization to SEQ ID NO's: 1 and 4. Claim 3 depends from claim 2 and the "natural, synthetic or half-synthetic" oligonucleotides that bind to SEQ ID NO: 1 and SEQ ID NO: 4 are limited to those oligonucleotides that would hybridize under the conditions set forth in claim 2. Mierendorf *et al.*, do not teach each and every limitation of Applicants invention and does not anticipate the instant invention.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

***Claim Rejections Under 35 U.S.C. § 112, First Paragraph***

Claims 2-6, 8-11, 17, 18, 20 and 24 are rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement.

The Examiner has rejected these claims as a "New matter rejection." Applicants respectfully traverse.

The Examiner asserts that the amendments in the previously filed Response constitute new matter for which support in the specification was not specifically indicated. The amendments, the Examiner is referring to in claims 2, 5 and 20 were as follows: "said partial sequence comprising more than 8 nucleotides", under conventional stringent hybridization conditions", and "more than 8 and up to 25 nucleotides."

Support for these amendments are found throughout the specification. For example, on page 2, paragraph [0006]-[0009]:

> [0006] Another solution to this object involves preparing an isolated nucleic acid that codes a protein, which is identical or similar to a protein that occurs naturally in human keratinocytes and is increasingly expressed when the keratinocytes are in an activated state, and which has the nucleotide sequence indicated in either the SEQ ID NO:1 sequence protocol or the SEQ ID NO:4 sequence protocol, or a nucleotide sequence complementary to one of these two, or a partial sequence of one of these two indicated or complementary nucleotide sequences, or a nucleotide sequence that hybridizes wholly or in part with one of these aforementioned nucleotide sequences, wherein "U" can take the place of "T" in these two sequence protocols. This group of nucleic acids or nucleotide sequences according to the invention also includes in particular splice variants and sense or anti-sense oligonucleotides, which hybridize with the nucleotide sequence indicated in the SEQ ID NO:1 sequence protocol or the SEQ ID NO:4 sequence protocol, preferably identical or complementary to at least one of these two.
>
> [0007] As a result, the invention also encompasses proteins or polypeptides of the kind mentioned at the outset, which have an amino acid sequence that results from such a splice variant, in particular the splice variant of an mRNA, which is identical or complementary to the nucleotide sequence indicated in the SEQ ID NO:1 sequence protocol or the SEQ ID NO:4 sequence protocol.

> [0008] The sense or anti-sense oligonucleotides according to the invention encompass at least 6, preferably 8 to 25 nucleotides.
>
> [0009] The term "hybridized" relates to the hybridization procedures known in the art under conventional, in particular also under highly stringent hybridization conditions. The expert selects the specific hybridization parameters based on the used nucleotide sequence and his or her general technical knowledge (compare: Current Protocols in Molecular Biology, Vol. 1, 1997, John Wiley & Sons Inc., Suppl. 37, Chapter 4.9.14).The nucleic acid(s) according to the invention can be obtained from both a natural source or synthetically or semi-synthetically. Its presentation as cDNA has proven to be particularly effective in practice.

Applicants disclosed the preferred length of the oligonucleotides; define the term conventional hybridization stringencies; and provide a reference that is known to one of ordinary skill in the art for determining the stringencies. On page 8, paragraph [0020]:

> [0020] Protein pKe#122 and the polypeptides related thereto, i.e., to the amino acid sequence indicated in the SEQ ID NO:2 sequence protocol or SEQ ID NO:3 sequence protocol, specifically the polypeptides that can be derived through substitution, deletion, insertion and/or inversion from one of these amino acid sequences according to SEQ ID NO:2 or SEQ ID NO:3, or that have an amino acid sequence resulting from a splice variant of an mRNA, which is identical or complementary to the nucleotide sequence indicated in the SEQ ID NO:1 sequence protocol or the SEQ ID NO:4 sequence protocol, or to a partial sequence of these nucleotide sequences, or at least hybridized, offer numerous applications in the area of dermatological research and development. In particular, antibodies can be developed against these polypeptides or proteins, which then can be correspondingly modified for use either as diagnostic or therapeutic agents, or as cosmetic agents ("cosmeceuticals"). (Emphasis added).

On page 15, paragraph [0036]:

> [0036] As a result with respect to the overall structure of the pKe#122 gene, or in general of a polynucleotide that codes for protein pKe#122, we find that this gene or polynucleotide has the nucleotide sequence indicated in the SEQ IN NO:1 sequence protocol or the SEQ IN

> NO:4 sequence protocol, or a partial sequence of one of these two nucleotide sequences, or encompasses a nucleotide sequence or consists of one that is complementary to one of these indicated nucleotide sequences or one of their partial sequences, or that this gene or polynucleotide is wholly or partially hybridized with the nucleotide sequence indicated in the SEQ ID NO:1 sequence protocol or the SEQ ID NO:4 sequence protocol or with a partial sequence of one of these two nucleotide sequences, or with a sequence complementary to these indicated nucleotide sequences or their partial sequences, wherein "U" can take the place of "T" in the SEQ ID NO:1 and SEQ ID NO:4 sequence protocols, and that an mRNA corresponding or homologous to a cDNA of approx. 4.8 kb is read from this gene or polynucleotide. (Emphasis added).

Applicants provide sufficient support for the amendments and as such in not new matter. In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

## CONCLUSION

In view of the foregoing, reconsideration and withdrawal of all rejections and allowance of the application with claims 2-6, 8-11, 17, 18, 20 and 24 are respectfully solicited. The amended claims set forth, herein, are merely to expedite prosecution and allowance of the application and is not to be construed as surrender of any subject matter in the instant application. Applicants hereby reserve the right to pursue the subject matter of the canceled claims in one or more continuations, continuation-in-part or divisional patent applications.

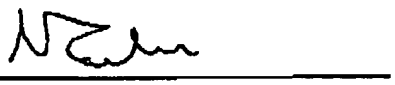
If there are any remaining issues or the Examiner believes that a telephone conversation with the Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at telephone number shown below.

Although, Applicants believe that no further extensions of time (beyond the two month petition) are required with submission of this paper, Applicants request that this submission also

be considered as a petition for any extension of time if necessary. The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for any retroactive extensions of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to Deposit Account No. 50-0951.

Respectfully submitted,

AKERMAN SENTERFITT



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